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(71) Applicant (for all designated States except US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **PHILLIPS, Eifion**
[GB/US]; AstraZeneca Wilmington, P.O. Box 15437,
Wilmington, DE 19850-5437 (US).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

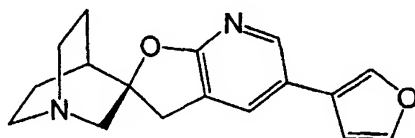
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/096912 A1

(54) Title: **NOVEL LIGAND FOR NICOTINIC ACETYLCHOLINE RECEPTORS USEFUL IN THERAPY**



(I)

(57) Abstract: A compound having the formula (I): and any pharmaceutically-acceptable salts thereof, and their uses in therapy and compositions containing them.

Novel ligand for nicotinic acetylcholine receptors useful in therapy

Technical Field

This invention relates to novel spiroazabicyclic heterocyclic amines or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. A further object is to provide active compounds which are potent ligands for nicotinic acetylcholine receptors (nAChR's).

Background Of The Invention

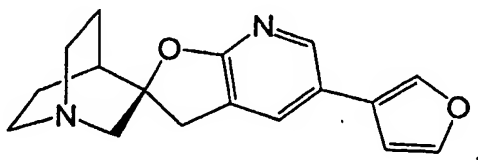
The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

US Patent 5,468,875 discloses N-alkylcarbamic acid 1-azabicyclo[2.2.1]hept-3-yl esters which are centrally active muscarinic agents useful in the treatment of Alzheimer's disease and other disorders.

N-(2-alkoxyphenyl)carbamic acid 1-azabicyclo[2.2.2]octan-3-yl esters are disclosed in Pharmazie, vol. 48, 465-466 (1993) along with their local anesthetic activity. N-phenylcarbamic acid 1-azabicyclo[2.2.2]octan-3-yl esters substituted at the *ortho* position on the phenyl ring are described as local anaesthetics in *Acta Pharm. Suecica*, 7, 239-246 (1970). Europyridines useful in controlling synaptic transmission are disclosed in WO 97/05139.

Summary of the Invention

The invention generally relates to a compound having the formula:

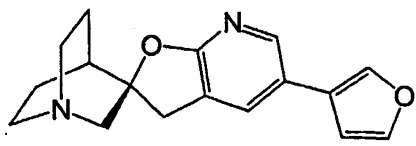


and any pharmaceutically-acceptable salts thereof, and their uses in therapy and compositions containing them.

Disclosure Of The Invention

One aspect of the invention is A compound having the formula:

5



and any pharmaceutically-acceptable salts thereof.

Another aspect of the invention relates to a pharmaceutical composition comprising a compound as described above, and a pharmaceutically-acceptable diluent or carrier.

10 Another aspect of the invention relates to the above pharmaceutical composition for use in the treatment of prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor beneficial.

Another aspect of the invention relates to the above pharmaceutical composition for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

15 Another aspect of the invention relates to the above pharmaceutical composition for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, or mania or manic depression Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from
20 exposure to products containing nicotine, pain, and for ulcerative colitis.

Another aspect of the invention relates to a use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial.

25 Another aspect of the invention relates to a use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

Another aspect of the invention relates to the above use, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder.

Another aspect of the invention relates to the above use, wherein the disorder is
5 anxiety, schizophrenia, or mania or manic depression.

Another aspect of the invention relates to the above use, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

Another aspect of the invention relates to the use of a compound as described above in
10 the manufacture of a medicament for the treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

Another aspect of the invention relates to a method of treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial
15 which comprises administering a therapeutically effective amount of a compound as described above.

Another aspect of the invention relates to a method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as described above.

20 Another aspect of the invention relates to the above method, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, or Attention Deficit Hyperactivity Disorder.

Another aspect of the invention relates to the above method, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative
25 disorders in which there is loss of cholinergic synapses.

Another aspect of the invention relates to the above method, wherein the disorder is anxiety, schizophrenia or mania or manic depression.

Another aspect of the invention relates to a method of treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction, pain, and for ulcerative colitis which
30 comprises administering a therapeutically effective amount of a compound as described above.

Pharmaceutical Compositions

A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of diluents and carriers are:

- for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;
- for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Utility

A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or

conditions; and a method of treatment or prophylaxis of one of the above mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically acceptable salt thereof, to a patient.

5 Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the $\alpha 7$ nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over compounds which are or are also agonists of the $\alpha 4$ nAChR subtype. Therefore, compounds
10 which are selective for the $\alpha 7$ nAChR subtype are preferred. The compounds of the invention are indicated as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit,
15 memory loss, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in
20 inducing the cessation of smoking, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

25 The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at $\alpha 7$ nAChR subtype

30 125 I- α -Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; MgCl_2 1; NaCl 120; KCl 5; pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 g, the supernatant was saved and

the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12000 g, washed, and resuspended in HB. Membranes (30–80 µg) were incubated with 5 nM [¹²⁵I]α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM CaCl₂ or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethylether)] for 2 hours at 21°C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per minute). Nonspecific binding was described by 100 µM (–)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the α4 nAChR subtype

[³H]-(–)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenized as in the [¹²⁵I]α-BTX binding assay, centrifuged for 20 minutes at 12,000 x g, washed twice, and then resuspended in HB containing 100 µM diisopropyl fluorophosphate. After 20 minutes at 4°C, membranes (approximately 0.5 mg) were incubated with 3 nM [³H]-(–)-nicotine, test drug, 1 µM atropine, and either 2 mM CaCl₂ or 0.5 mM EGTA for 1 hour at 4°C, and then filtered over Whatman glass fibre filters (thickness C) (pretreated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 µM carbachol, and specific binding was typically 84%.

Binding data analysis for Tests A and B

IC₅₀ values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding K_D values of 1.67 and 1.70 nM for the ¹²⁵I-α-BTX and [³H]-(–)-nicotine ligands respectively. K_i values were estimated using the general Cheng-Prusoff equation:

$$K_i = [IC_{50}] / ((2 + ([ligand]/[K_D])^n)^{1/n} - 1)$$

where a value of n=1 was used whenever n_H<1.5 and a value of n=2 was used when n_H≥1.5. Samples were assayed in triplicate and were typically ±5%. K_i values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 1000 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

Examples

Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer and are reported as m/z for the parent molecular ion with its relative intensity. Room temperature refers to 20–25°C.

For additional examples and precursors, see published application WO 99/03859.

Example 1A

5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (100 mg, 0.462 mmol) and sodium acetate (410 mg, 5 mmol) in 50 % aqueous acetic acid (4mL) was heated to 60°C. Bromine (0.100 mL, 1.94 mmol) was added via a syringe over 10 minutes, and the solution was then heated under reflux for 1 hour. The mixture was allowed to cool to ambient temperature, basified to pH >10 with sodium carbonate, and extracted with chloroform (3 x 15 mL). The combined extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to give the title compound (110 mg, 0.37 mmol, 81 %) as an off-white solid: electrospray MS 295 ([MH]⁺, with ⁷⁹Br, 100), 297 ([MH]⁺, with ⁸¹Br, 98).

Example 1B

(R)-(-)- 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The enantiomer (R)-(-)-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (1.95 g, 9 mmol) treated in the same way as described in example 2A provided the title compound (1.77 g, 6 mmol, 67%) ([α]²³ = -45.5 ° (c = 1, MeOH)).

Example 2

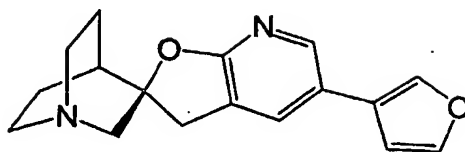
(2'R)-5'-(2-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(2'R)-5'-bromo-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (0.70 g, 2.37 mmol), 3-furylboronic acid (0.39 g, 3.5 mmol), tetrakis(triphenylphosphine)palladium (0) (131 mg, 0.11 mmol), and sodium carbonate (0.75 g, 7.1 mmol) were placed in a tube under nitrogen. Water (3 ml), ethanol (3 ml) and tetrahydrofuran (12 ml) were added. The mixture was then heated at 70 °C and stirred under nitrogen for 24 h. The mixture was then evaporated under vacuum and the residue from evaporation was partitioned between dilute

aqueous sodium hydroxide and chloroform, the layers were separated, and the aqueous layer was further extracted with chloroform. The chloroform extract was dried (magnesium sulfate), filtered, and evaporated. The residue was purified by reverse phase HPLC on a Waters Novapak-HR C₁₈ Column using a gradient of 0-70% acetonitrile / water (each solvent containing 0.1% trifluoroacetic acid as a buffer) as the eluant. The product-containing fractions were evaporated, then the residue was dissolved in methanol. Excess concentrated hydrochloric acid was added, and the solution was evaporated to give the dihydrochloride salt of the title compound (489 mg) as a colourless solid; m.p. 223-225 °C (decomp.); m/z 283 (100%, MH⁺).

CLAIMS

1. A compound having the formula:



and any pharmaceutically-acceptable salts thereof.

2. A pharmaceutical composition comprising a compound as described above, and a pharmaceutically-acceptable diluent or carrier.

3. The pharmaceutical composition according to Claim 2 for use in the treatment of prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor beneficial.

4. The pharmaceutical composition according to Claim 2 for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

5. The pharmaceutical composition according to Claim 2 for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, or mania or manic depression Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

6. Use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial.

7. Use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

8. The use according to Claim 7, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder.

9. The use according to Claim 7 wherein the disorder is anxiety, schizophrenia, or mania or manic depression.
10. The use as claimed in claim 7 wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is
5 loss of cholinergic synapses.
11. Use of a compound as described above in the manufacture of a medicament for the treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.
12. A method of treatment or prophylaxis of human diseases or conditions in which
10 activation of the $\alpha 7$ nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound as described above.
13. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as described above.
14. The method according to Claim 13, wherein the disorder is Alzheimer's disease,
15 learning deficit, cognition deficit, attention deficit, memory loss, or Attention Deficit Hyperactivity Disorder.
15. The method according to Claim 13, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is
20 loss of cholinergic synapses.
16. The method according to Claim 13, wherein the disorder is anxiety, schizophrenia or mania or manic depression.
17. A method of treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction, pain, and for ulcerative colitis which comprises administering a therapeutically
25 effective amount of a compound as described above.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01031

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 491/22, A61K 31/439, A61P 25/00, A61P 1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9903859 A1 (ASTRA AKTIEBOLAG), 28 January 1999 (28.01.99), see specially example 21 --	1-17
X	WO 0042044 A1 (ASTRAZENECA AB), 20 July 2000 (20.07.00) --	1-17
X	WO 9854189 A1 (NEUROSEARCH A/S), 3 December 1998 (03.12.98) --	1-17
A	J. Med. Chem., Volume 39, 1996, Gunnar Nordvall et al: "3-(2-Benzofuranyl)quinuclidin-2-ene Derivatives: Novel Muscarinic Antagonists", page 3269 - page 3277 --	1-17

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 Sept 2002

Date of mailing of the international search report

26-09-2002

Name and mailing address of the ISA/
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Facsimile No. +46 8 666 02 86

Authorized officer

Viveca Norén/Eö
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12-17
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☒ Claims Nos.: 6-7, 12-13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01031

Box I.1

Claims 10-12 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Box I.2

The formulations "diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial" and "psychotic disorders or intellectual impairment disorders" can not be considered to be clear and concise as they do not clearly define the intended diseases and conditions. Hence claims 6-7 and 12-13 do not fulfil the demands of PCT article 6. The search has therefore mainly been performed on the diseases and conditions specified in claims 8-11 and 14-17.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/09/02

International application No.
PCT/SE 02/01031

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9903859 A1	28/01/99	AU 739022 B	04/10/01
		AU 8367998 A	10/02/99
		BR 9810924 A	15/08/00
		CN 1270592 T	18/10/00
		EE 200000031 A	16/10/00
		EP 0996622 A	03/05/00
		EP 1213291 A	12/06/02
		HU 0003844 A	30/07/01
		IL 134086 D	00/00/00
		JP 2001510194 T	31/07/01
		NO 20000226 A	14/03/00
		NZ 502298 A	01/02/02
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		SE 9702746 D	00/00/00
		SK 183599 A	14/08/00
		TR 200000129 T	00/00/00
		US 6110914 A	29/08/00
		US 6369224 B	09/04/02
		ZA 9805995 A	03/08/99
		SE 9800977 D	00/00/00
		WO 9961990 A	02/12/99
WO 0042044 A1	20/07/00	AU 2334300 A	01/08/00
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